UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,876	06/20/2005	Christine Power	SLII-P01-001	6247

28120 7590 11/07/2007

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
DEBERRY, REGINA M	
ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
11/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,876	POWER ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-51* is/are pending in the application.

4a) Of the above claim(s) *35-41,43-47 and 49-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-34 and 42-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/05,3/07,9/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendments filed 08 October 2004 and 20 June 2005 have been entered in full. Applicant's election of Group I (claims 26-34, 42-48) in the reply filed on 31 August 2007 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 35-41, 43-47, 49-51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 31 August. Claims 26-34, 42-48 are under examination.

Information Disclosure Statement

The information disclosure statement(s) (IDS) filed 20 June 2005, 23 March 2007 and 04 September 2007 and the IDS letter, filed 30 October 2007, were received and comply with the provisions of 37 CFR §§1.97 and 1.98. They have been placed in the application file and the information referred to therein has been considered as to the merits.

Sequence Rules

The specification is not in compliance with 37 CFR 1.821-1.825 of the Sequence Rules and Regulations. When the description of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph

(c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier (SEQ ID NO:), in the text and claims of the patent application. 37 CFR 1.821(a) presents a definition for nucleotide and/or amino acid sequences. This definition sets forth limits in terms of numbers of amino acids and/or numbers of nucleotides, at or above which compliance with the sequence rules is required. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. Please see MPEP section 2422.01.

The specification refers to a sequence on page 19, line 27 and on page 30, line 9 but does not identify the sequences by their sequence identifiers. The entire specification must be examined for proper sequence identifiers. Sequences appearing in drawings should be referenced in the corresponding Brief Description thereof. See 37 C.F.R. §1.58(a) and §1.83. Appropriate correction is required.

Applicant must submit a response to this Office Action and compliance with the sequence rules within the statutory period set for response to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-34, 42-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 (and dependent claims 27-34, 42-48) is drawn to a mutein of any of (a) to (d) which is encoded by a DNA sequence which hybridizes to the complement of the DNA sequence encoding any of (a) to (d) under moderately stringent conditions or under highly stringent conditions. Stringency is relative, and the art does not recognize a single set of conditions as stringent. The specification also does not provide an unambiguous definition for the term. In the absence of a recitation of clear hybridization conditions (e.g., "hybridizes at wash conditions of A X SSC and B % SDS at CoC"), the claims fail to define the metes and bounds of the varying structures of polynucleotides recited in the claimed methods.

Furthermore, claim 42 is indefinite because of the recitation, "produced by a cell". It is unclear if the instant claim encompasses a substance being produced by a transgenic animal or produced recombinantly. If the latter case is correct, amending the claim to recite, "produced by an isolated cell" would be remedial.

Lastly, claim 48 is indefinite because it depends from withdrawn claim 35 and thus it is unclear what the instant claim encompasses. The metes and bounds cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-34, 42-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a method for treating a fibrotic disease comprising administering to a patient in need of treatment therefore a therapeutically effect amount of a substance comprising a **polypeptide comprising SEQ ID NO:2 or SEQ ID NO:4**

does not reasonably provide enablement for:

a method for **preventing** a fibrotic disease comprising administering to a patient in need of treatment therefore a therapeutically effect amount of **a polypeptide comprising amino acid 22 to 401 of SEQ ID NO:2 or SEQ ID NO:4; a polypeptide comprising amino acid residues 22 to 194 of SEQ ID NO:2 or SEQ ID NO:4; a mutein of any of (a) to (d), wherein the amino acid sequence has at least 40% identity to at least one of the sequences in (a) to (d); a mutein of any of (a) to (d) which is encoded by a DNA sequence which hybridizes to the complement of the DNA sequence encoding any of (a) to (d) under moderately stringent conditions or under highly stringent conditions; a mutein of any of (a) to (d) wherein any changes in the amino acid sequence are conservative amino acid substitutions to the amino acid sequences in (a) to (d) or a salt or an isoform, fused protein, functional derivative, active fraction or circularly permutated derivative of any of (a) to (g).**

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification states that the present invention is in the field of fibrotic diseases and connective tissue disorders. More specifically, the invention relates to the use of osteoprotegerin (OPG) for the treatment and/or prevention of fibrotic diseases, in particular scleroderma. The specification states that fibrosis is a condition relating to an overproduction of collagen e.g. in the internal organs, including the kidneys, heart, lungs, stomach and joints (page 1, lines 20-21). The specification teaches that scleroderma is a disease of the connective tissue characterized by fibrosis of the skin and internal organs, leading to organ failure and death (pages 3-4). The specification teaches the sequences of OPG as SEQ ID NOs:2 and 4 (page 10). The specification teaches that lung fibrosis induced in mice by intra-tracheal administration of bleomycin was successfully treated with OPG (page 38).

The disclosure fails to enable an artisan to make and use the genus. The disclosure fails to teach an artisan how to make and use the whole genus (i.e. not only the amino acid sequence of SEQ ID NO:2, 4), because the majority of the species of the genus do not comprise just SEQ ID NO:2 or 4. It would require an indeterminate quantity of fundamentally unpredictable investigational experimentation of the skilled artisan to determine whether any modified polypeptide (as recited in the instant claim 26) could be used in the same manner as the native exemplar (treatment of fibrotic disease). OPG is a protein known to have a role in the development of bone. Simonet

et al. (reference submitted by Applicant, Cell 89:309-319, 1997) teach specific regions of amino acid residues that are important for OPG bone activity. Simonet et al. fail to disclose biological activity of muteins, salt or isoforms, fused proteins, functional derivatives, active fractions or circularly permutated derivatives of OPG in any of the bone assays. Moreover, the instant specification states that OPG has not yet been suggested to be involved in fibrotic diseases. The purported novelty is OPG's therapeutic properties in fibrotic disease. Applicant has provided no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the OPG protein which are tolerant to change and the nature and extent of changes that can be made in these positions of the **claimed activity (i.e. that activity coupled with fibrotic disease treatment)**. Specific regions that are important for bone activity have been identified in OPG, but there is no evidence that the active site for bone activity is also the active site for fibrotic disease activity. For example, Sato et al. (The EMBO Journal, Vol. 12, No. 11, pages 4181-4189, 1993) teach a receptor where different activities have been mapped within the protein. Sato et al. teach two distinct cytoplasmic regions in the same beta subunit receptor, which are responsible for different signals. Mutations made in the beta subunit affected some signaling pathways but not others (see abstract and Figure 10). OPG is a decoy receptor for OPG ligand. The specification and prior art fail to teach the regions of OPG that are involved in fibrotic diseases or that the active site for bone activity is also the *same active site* for fibrotic disease activity. There are no working examples demonstrating the administration of mutated/derivatives of OPG for

the treatment of fibrosis. Thus, the evidence with respect to the recited variants of OPG is not commensurate in scope with these claims, which is directed to a different activity. Lastly, the specification is not enabling because of the claim limitation "preventing". Prevent means to completely stop a disease/condition from occurring. "Prevention" is not a relative term, it is total. A very high degree of evidence is required, which is accepted in the art, that an absolute protection from the pathology exists over an extended period of time.

Due to the large quantity of experimentation necessary to show that the onset of a fibrotic disease has been prevented, the large quantity of experimentation necessary to generate the number of derivatives recited in the claims and screen same for activity (treatment of fibrotic disease), the lack of direction/guidance presented in the specification regarding same and regarding which structural features in OPG that are required to provide claimed activity, the absence of working examples directed to same, the complex nature of the invention, and the breadth of the claims which fail to recite any structural limitations and parameters regarding prevention of a fibrotic diseases, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections-35 USC § 102(e)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent

granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 26-34, 42 and 48 are rejected under 35 U.S.C. 102(e) as being anticipated by Dunstan, US 2006/0019887 A1. The instant specification teaches fibrosis as a condition relating to an overproduction of collagen e.g. in the internal organs, including the kidneys, heart, lungs, stomach and joints (page 1, lines 20-21). The specification teaches scleroderma as a disease of the connective tissue characterized by fibrosis of the skin and internal organs (page 4, lines 6-10).

Dunstan teaches the administration of OPG for the treatment of fibrous dysplasia (para 0110). Dunstan teaches human OPG sequence (paras 0015-0025). Dunstan teaches the fusion of OPG with an Fc region (paras 0029-0036). Dunstan teaches the recombinant expression of OPG in host cells (paras 0082-0089). Dunstan teaches that OPG can be coupled to PEG (para 0107). Dunstan teaches that OPG can be glycosylated (paras 0030, 0080, 0082, 0089). Dunstan teaches the delivery of OPG polypeptide with endothelin-1 (e.g. anti-scleroderma agent) (para 0149).

Claims 26-34, 42 and 48 are rejected under 35 U.S.C. 102(e) as being anticipated by Boyle et al., U.S. 7,005,413 B1. Boyle et al. teach human osteoprotegerin (OPG) polynucleotide and polypeptides and host cells for expressing OPG (column 2, lines 45-55; column 7, line 60-column 8, line 11; column 31, lines 47-67). Boyle et al. teach monomers and dimers (column 8, lines 60-67) and glycosylation of OPG (column 24, lines 4-15). Boyle et al. teach the administration of OPG with prostaglandins (e.g.

anti-scleroderma agent) (column 2, line 66-column 3, line 14). Boyle et al. teach that OPG can be linked to PEG or an Fc region (column 27, lines 23-47 and column 30, lines 32-42). Conditions treatable with OPG include Paget's disease of bone (osteitis dermans)(column 34, lines 32-43). The Online Medical Dictionary teaches Paget's disease as a disease of the bone that initially results in the excessive resorption of bone followed by the replacement of normal bone marrow with vascular and fibrous tissue. See Attachment (Appendix A).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 26-34 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 32-66 of copending Application No. 10/966,845 in view of Franklin, Biochemical Pharmacology, Vol. 49, No. 3, pages 267-273 (1995).

The claims of the instant application are drawn to a method for treating and/or preventing a fibrotic disease comprising administering OPG (SEQ ID NO:2 or SEQ ID NO:4) to a patient. Claims 32-66 of copending Application No. 10/966,845 (US Patent Application 2005/0143301) are drawn to a method of treating and/or inhibiting progression and/or symptoms of a fibrotic disease, fibrotic diseases of the liver, kidney, lung and inflammation comprising administering OPG (SEQ ID NO:2 or SEQ ID NO:4) to patient. Although the conflicting claims are not identical, they are not patentably distinct from each other. Franklin teaches that progressive fibrosis of organs and a tissue, including the liver, lungs, kidneys, heart, blood vessels and skin, comprises a constellation of mechanistically related disorders. Franklin states that each of the disorders shares the common feature of a progressive and inappropriate accumulation of connective tissue, dominated by collagen, which leads to disorganization of normal tissue architecture and consequent loss of function (page 267, 1st paragraph). Franklin teaches that in conditions where the primary tissue-damaging cause persists, the inflammatory response becomes chronic, thus perpetuating the drive to fibrogenesis (page 268, 1st paragraph).

It would have been obvious to modify the method of treating and/or preventing a fibrotic disease to include treatment of fibrotic diseases of the liver, kidney, lung and inflammation, as recited in co-pending application 10/966,845 because Franklin teaches that progressive fibrosis of organs and tissues comprises a collection of mechanistically related disorders, which share the common feature of a progressive and inappropriate accumulation of connective tissue.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
Primary Examiner, Art Unit 1647

RMD
11/5/07